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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/654,116	08/30/2000	A. Charles Morgan JR.	180042.418C2	6638

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EXAMINER
DUFFY, PATRICIA ANN

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/654,116	Morgan et al
Examiner	**Art Unit**
Patricia A. Duffy	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 10, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4, 19, and 21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 19, and 21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The amendment filed 12-10-02 has been entered into the record. Claims 1-4, 19 and 21 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. The rejection of claims 1-4 and 19 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn based on Applicants amendments to the claims.

4. Claims 1-4 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendment to the claims and in view of the new rejections set forth below based on Applicants' amendment to the claims.

5. Claims 1-4 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the amendment to the claims and in view of the new rejections set forth below based on Applicants' amendment to the claims.

Rejections Maintained

6. Claim 2 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "small" in claim 2 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicants assets that this is a term of art that would be readily understood by persons of the art. This is not persuasive, small is neither defined by the art nor this specification.

7. Claims 1, 2, 3, 4 and 19 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Marcoullis et al, (British Journal of Haematology, 43(1):15-26, 1979) is maintained for reasons made of record in Paper No. 9, mailed 6-10-02.

Applicants arguments have been carefully considered but are not persuasive. Applicants argue that antibodies are not small molecules. This is not persuasive, small is a relative term and the metes and bounds of this term is not established in the art nor in the specification and therefore antibody meets the limitation of "small". Applicants argue that Marcoullis et al describe an IgM fraction that is not isolated. This is not persuasive, Marcoullis et al describe isolated and purified IgG and IgM fractions that bind TCII from a patient. Marcoullis et al teach that the isolated and purified IgG from the patient provided for antibodies that bind TCII and neutralized the binding of vitamin B12. As such, these antibodies necessarily have the property of blocking vitamin B12 uptake since they block binding to TCII which is the protein responsible for mediating the uptake of vitamin B12. Marcoullis et al teach that the presence of blocking and binding antibodies

has been associated with increased cobalamin (vitamin B12) levels. As such, the IgG antibodies of Marcoullis et al necessarily possess the function of inhibiting cellular uptake of vitamin B12 as claimed and would be recognized by one of skill in the art. Further, Since the Office does not have the facilities for examining and comparing applicant's antibody or antibody derivative with the antibody molecule of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the recited antibody or derivative directed to TcII does not possess the same functional characteristics). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

8. Claims 1 and 2 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Shimizu et al, (Oncology, 44(3):169-73, 1987) is maintained for reasons made of record in Paper No. 9, mailed 6-10-02.

Applicants arguments have been carefully considered but are not persuasive. Applicants argue that the reference does not teach that methyl-B12 is directed to TCII. This is not persuasive, B12 and derivatives there of inherently bind TCII and therefore meet the limitation of "directed to". TCII is responsible for binding vitamin B12 and mediating the cellular uptake. Therefore, derivatives of B12 that are directed to TCII, necessarily prevent cellular uptake of vitamin B12 as claimed. Since the Office does not have the facilities for examining and comparing applicant's small organic molecule with the molecule of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the recited vitamin B12 derivative directed to TcII does not possess the same functional characteristics). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

New Rejections Based on Amendment

9. Claims 1-4, 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants have broadened the scope of the claim by deleting language that the agent is directed to a vitamin B12 binding cite and is capable of competitively antagonizing or modulating said binding site. The claim now recites a genus of growth blocking agents directed to TCII that merely function to inhibit the cellular uptake of Vitamin B12. Applicants have not pointed to the specification by page and line number where written description for this new genus resides and asserts generic specification provides support. This is not persuasive with respect to the genus claims now presented. Figure 4 provides for particular types of reagents, however this Figure does not convey the generic agents directed to TCII, but specific type of reagents that are targeted to specific areas on TCII and are limited to antibodies. As such, this Figure can not support the genus of growth inhibiting agents directed to TCII. There is no conception by way of written description of agents generically "directed to TCII" in this specification as originally filed.

10. Claims 1-4, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are broadly drawn to any growth blocking agent "directed to" TcII, the agent being capable of inhibiting the cellular uptake of vitamin B12. The claims further limit the agent to proteins, peptides, small organic molecules and antibodies.

The specification fails to provide any written description of any small organic molecule or peptide that is a growth blocking agent that directed TcII, the agent being capable of inhibiting the cellular uptake of vitamin B12. There is no description of any peptide or small organic molecule with these functional properties. There is no description of any genus of proteins or polyclonal antibody with these functional properties. Applicants are claiming all functional equivalents, when the specification fails to disclose even one agent that possesses all the functional requirements of the claim (i.e. growth blocking, directed to TcII, and inhibits cellular uptake of B12. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. The claims encompass a myriad of functional equivalent variants of small molecules, proteins and peptides and polyclonal antibodies that have no structure in common. The genus of such functional equivalent variants is incalculable and this specification fails to provide clear written description of a

single agent that meets the claimed polyclonal antibody, small organic molecule or peptide that has basic function as recited in the claims. The disclosure fails to meet the most basic requirement of written description for the claimed invention for the claimed subject matter.

Applicants arguments with respect to the previous rejection of record are not persuasive. Applicants argue that the specification provides sufficient identifying characteristics to demonstrate to the skilled artisan that Applicants were in possession of the claimed invention. This is not persuasive, Applicants specification is devoid of any small organic molecule or peptide or protein or polyclonal antibody that functions as claimed. Applicants specification is devoid of any written description of starting material for such.

There is no defined chemical structure in the claims that relates to "directed to TCII" and as such, description of a monoclonal antibody does not provide written description support for the claimed genus and specifically claimed subgenera of small organic molecules, peptides, proteins and antibodies (i.e. polyclonal).

11. Claims 1-4, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to any growth blocking agent directed to TcII, the agent being capable of inhibiting the cellular uptake of vitamin B12. The claims further limit the agent to proteins, peptides, small organic molecules and antibodies. The claims encompass of myriad of molecular entities, which in turn encompass of myriad of diverse biochemical properties. The specification fails to teach what residues on TcII are responsible for the ability of some monoclonal antibodies to inhibit cellular uptake of

vitamin B12. Further, the specification specifically teaches that mere binding (a.k.a. "directed to") of an antibody does not predict the function of inhibiting cellular uptake (see page 38, and Figure 6). As such, mere binding or targeting or "directing to" does not predictability relate to inhibition as claimed. One skilled in the art would be unable to predict what potential binding sites would be appropriate to target for the identification of small molecules, peptides, or other proteins, antibodies as specifically claimed. The specification fails to teach even a single beginning small organic molecule, peptide or protein other than specifically identified monoclonal antibodies could be "directed to" TCII and function as claimed. Without out guidance as to the structure of such molecules that are directed to TcII, and no starting point for experimentation, one of skill in the art would have no direction or guidance to screen for potential candidates. The specification fails to teach even a beginning point for experimentation with respect to genus of proteins, peptides and small organic molecules that are "directed to" TcII and function as claimed. The binding site of the monoclonal antibodies that inhibit in Figure 6 has not been disclosed by Applicants. It has been well established in the art that screening of agents that bind to receptors, or in this case agents that bind to binding proteins, do not have the ability to determine agonists versus antagonist function, and the art establishes difficulty of excluding "non-specific" inhibition of receptor binding (page 102, first full paragraph, Burch, R.M.., Journal of Receptor Research, 11(1-4):101-113, 1991). The state of the art does not allow for accurate design of molecules based solely on function and an undisclosed binding site (vitamin B12 binding site on TcII). Rudinger et al "Peptide Hormones" ed by Parsons et al, University Park Press June 1976, pages 1-7, especially page 6, teaches that "the significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case

by painstaking experimental study.". Kuntz et al (Science 257:1078-1082, 1992) discloses that with current technology scientists can not yet design drugs from "first principles" (e.g. page 1078, left column). Though Kuntz et al disclose a particular computational cycle used to combine structural information regarding complemenatrity between designer drug and target, the method (a) uses X-ray crystallographic or computer generated structural data not set forth in this specification and are known in the art to involve non-routine experimentation and/or results of such are not predictive of *in vivo* activities, (b) of the 100,000 molecules modeled, only 2-20% of 10-50 compounds might show the predicted biological properties, and © the method is characterized by Knutz et al as "problematic" in optimizing leads (e.g. due to difficulties in obtaining proper ligand conformation and discriminating among several proposed interaction modes of similar energy (see e.g. 1059-1061 "Structure-based design"). Further, the same authors question whether the technique will work for compounds other than peptides and oligonucleotides (e.g. page 1061, left column "...it is possible to adapt...) and the algorithm is designed for enzyme inhibitors, in contrast to the instant invention. The assays disclosed in the specification do not provide for all the functional information recited in the claims. The courts have held that "... whenever there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement." *Genetech Inc. v. Novo Nordisk A/S* 42USPQ2d 1001. In the instant case, the specification fails to provide disclosure of any specific starting material with respect to small organic molecules,

peptides and proteins with respect to products other than specifically identified monoclonal antibodies.

In the absence of further guidance from Applicants relating to the above noted deficiencies, it would require undue experimentation to make and use the claimed growth blocking agents as claimed.

Applicants' arguments with respect to the previous rejection of record are not persuasive. Applicants argue that successful working examples of screening methods. This is not persuasive there is absolutely no written description or guidance on how to make small molecules, peptides, proteins and polyclonal antibodies that are directed to TCII and inhibit as claimed. There is absolutely no guidance on how to make these compounds prior to screening. There is absolutely no written description of any starting material and as such screening becomes undue. Further, the specification must enable the invention at the time that it was made. The fact that none are described and screening is required to describe any molecules that fall within the genus supports the position of the examiner with respect to the position held by the court in *Genetech Inc. v. Novo Nordisk A/S* 42USPQ2d 1001. Applicants arguments with respect to monoclonal antibodies are respectfully noted, however claims 1-4 and 19 are not so limited.

12. Claims 1-4 and 19 and new claim 21 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims growth blocking agent that is "directed to" TcII. The metes and bounds of "directed to TCII" as now recited can not be readily ascertained. The specification does not define "directed to" and directed is conventionally defined as subject to supervision or regulation or having positive or negative sense and therefore, neither the

claims nor the specification teaches the metes and bounds of the direction of these agents with respect to TcII, as such the metes and bounds of agents "directed to" this site as claimed can not be readily ascertained.

13. Claims 1, 2, 3, 4, 19 and 21 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Carmel et al (Proceedings of the Society for Experimental Biology and Medicine, 188:77-81, 1988; reference AG on PTOL-1449 of record).

Carmel et al teach monoclonal antibody IgG antibody 16.6 that binds to human transcobalamin II (TcII) and inhibits the TCII-mediated uptake of cobalamin by K562 cells (see page 80, column 2, lines 16-20). Because this monoclonal antibody binds and inhibits the uptake of vitamin B12, it necessarily is a growth inhibiting agent as claimed. Since the Office does not have the facilities for examining and comparing applicant's claimed monoclonal antibody with the molecule of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that antibody of the prior art directed to TcII does not possess the same functional characteristics). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Status of Claims

14. All claims stand rejected.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703).308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
February 21, 2003

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600